UNSATURATED AMINES
Investigation of the Reaction of Secondary Aliphatic Amines with Aldehydes

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PREFACE

Procedures recorded in this dissertation are given in detailed form to facilitate duplication by other investigators. There is some repetition of certain data on successive pages to allow the assembling of related facts for ready reference.

All temperatures listed are in degrees Centigrade; the symbol therefor is omitted.

The boiling points are corrected values, unless otherwise noted; they represent boiling points at atmospheric pressure except where specific reduced pressure is listed. The thermometers used to obtain the corrected temperatures were calibrated against a set of thermometers standardized by the Bureau of Standards.

Melting points were determined in a copper block equipped with a thermometer similarly calibrated.

Pressure readings below 10 mm. were determined by means of a Stokes McLeod gauge; readings above 10 mm., by means of a Zimmerli gauge calibrated at 2 mm. against the McLeod gauge.

Fractionations were carried out through a 90 cm. column (of 2 cm. bore) packed with one-fourth inch Berl saddles and surrounded by a heated jacket. Some of the re-distillations were made through a similar column packed with stainless steel sponge.

Refractive indices were recorded at 25° ($\pm$ 0.1°) by means of a Bausch and Lomb Abbe Refractometer.

The atomic refractions of both F. Eisenlohr (as tabulated by A. Weissberger, "Physical Methods of Organic Chemistry", Vol. I, 1st Ed.,

p. 673, (1945), Interscience Publishers, Inc., New York, N. Y.) and A. Vogel (J. Chem. Soc. 1948, 1842) were employed in the calculation of molar refractions. Values determined by the use of the former are designated "(E)"; those by use of the latter, "(V)".

References are listed as is customary in technical works. Journal abbreviations are the official ones of Chemical Abstracts.

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Chapter I

INTRODUCTION AND REVIEW OF THE LITERATURE

The investigations described in this dissertation were begun under the sponsorship of the Office of Naval Research. The early work was carried out in accordance with the specified desire to prepare amines, liquid at room temperature, which contained one, or more, unsaturated carbon chains and two, or more, nitrogen atoms. Alternately, the compounds might be composed of two, or more, unsaturated carbon residues and one, or more, nitrogen atoms. No aromatic structures or imine linkages were to be present, and only atoms of carbon, hydrogen, and nitrogen were to appear in the finished products. (Later, the project was extended to include the ether-oxygen linkage as exhibited in the amino-ethers.)

Termination of the contract with the Office of Naval Research allowed some widening of the scope of the research so that the study of some solid unsaturated amines might be undertaken.

Since some of the first syntheses involved the reaction of unsaturated secondary amines and formaldehyde to yield methylenediamines having the specified characteristics, it was decided to direct the course of the investigation so as to determine what types of unsaturated compounds could be prepared by the interaction of secondary aliphatic amines and various aldehydes. In the past, the prevalence of side-reactions, the tendency of the reactants to form resins, as well as the lack of a commercial supply of intermediate materials, had discouraged research in this field.

FORMALDEHYDE

As previously mentioned, secondary amines react with formaldehyde to yield methylenediamines according to the equation:

$$R_2NH + HCHO + HNR_2 \rightleftharpoons R_2N-CH_2-NR_2 + H_2O$$

Theoretically, the use of ammonia rather than amines in this reaction should yield the parent compound, methylenediamine ($H_2N-CH_2-NH_2$); however, this substance appears to exist as the free base only in solution, where it is in equilibrium with the reactants, ammonia and formaldehyde. Its salts are stable but cannot be prepared in a direct manner. They have been synthesized by acid hydrolysis of methylenediformamide (1) which had been prepared by the condensation of two moles of formamide and one mole of formaldehyde. Recent investigation into the course of another formaldehyde reaction, that with nitramide (H_2N-NO_2) and amines to form 1,5-endomethylene-3,7-dinitro-1,3,5,7-tetrazacyclooctane, has brought forward the hypothesis that methylenediamine may there exist as a reaction-intermediate (2).

The simple aliphatic methylenediamines may be prepared directly; several literature references to them appear prior to 1900 (3,4,5,6). Henry was the first to synthesize and report the tetramethyl-, tetraethyl-, and tetra-n-propyl- derivatives as a group (6). These compounds resulted when the appropriate secondary amines were mixed with formaldehyde in aqueous solution. Isolation of the products was easily accomplished since their solubility in water was less than that of the original amines; they could, therefore, be "salted out" by the addition of

alkali, or extracted with a solvent such as benzene or diethyl ether. Once dried, they could be purified by distillation.

This reaction of two moles of amine with one mole of formaldehyde may be considered a type of "Mannich Reaction"; in this case the active hydrogen compound is the second mole of amine. It is to be expected, therefore, that some syntheses might be carried out in non-aqueous systems. Alcohols, as well as nitrobenzene and nitromethane (7), have been used successfully as solvents where an anhydrous medium was desired and where paraformaldehyde (trioxymethylene) served as the source of formaldehyde (8).

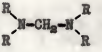
The early investigators characterized the simple aliphatic methylenediamines as pungent liquids which were stable in the absence of atmospheric moisture. However, reflux in acidic aqueous solution turned the course of the reaction back in the direction of the starting materials, yielding the aldehyde and the acid salt of the amine. Reaction with cyanogen bromide was generally found to give formaldehyde, the amine hydrobromide, and dimethylcyanamid (9). Treatment of the methylenediamines with formic acid split the molecules to yield both the original secondary amine and the methylated tertiary amine (10). Similarly, methylenediamines in the presence of acid, and at temperatures ordinarily not above 100°, have been used as dehydrogenating agents; in this case they are again decomposed into the original secondary amine and the methylated tertiary amine (11). At least one of the methylenediamines has been successfully nitrated (12); but they are apparently unattacked by sodamide even after twenty-four hour contact in an autoclave at ordinary pressure (13).

Some quaternary compounds have been formed by the interaction of aliphatic halides with the methylenediamines (9). The acid salts cannot be formed, however, because of their ready hydrolysis.

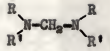
Stewart and Aston (14) reported that a diamine of this type behaved as a typical base, tetraethylmethylenediamine exhibiting base strength equivalent to that of diethylamine. Raman spectra of both the tetramethyl- and tetraethyl- derivatives have been examined (15).

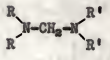
Synthesis of some of the members of this family of compounds by methods other than direct formaldehyde-amine interaction are reported in several instances. Aldehyde-bisulfite addition compounds have been substituted for the aldehyde (16), methylene halides have been used to supply the methylene group (17,18), spontaneous intermolecular reaction of chloromethyl derivatives of secondary amines (19), interaction of chloramines and amine Grignard reagents (20), and hydrolysis of the quaternary salts of cyclic trimethylenetriamines (21) have produced compounds of this structure.

Many of the methylenediamines reported to date are completely symmetrical, having identical carbon chains attached to each of the two nitrogen atoms:

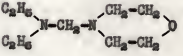


However, modifications in synthesis have allowed the introduction of differing radicals into the same molecule. Two types are:

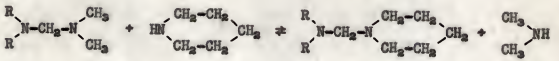
I.  (21,22)

II.  (23,24,25,26)

In compounds of type II the two "R" groups may be part of a single cyclic structure wherein the nitrogen is one of the hetero-atoms of the original amine. An example of such a compound is diethylaminomethylmorpholine (23,24):



Several investigators have found that "exchange" or "transposition" reactions occur rather readily with methylenediamines as well as with the Mannich Bases (27,28). The dimethylamino- group has been replaced by the morpholino- or piperidino- radical by simply refluxing the diamine with an equimolar quantity of the other amine; e. g.



In recent years, some industrial use has been made of the aliphatic methylenediamines: rust preventives in turbine oils (23), hardening and tanning agents (29), and solubilizers and demulsifiers for crude

oil emulsions (30).

However, it has been in the recent attempts to elucidate the course of the Mannich Reaction that the methylenediamines have achieved their greatest importance.

Mannich observed in 1912 that the reaction of antipyrine salicylate, formaldehyde and ammonium chloride yielded a tertiary amine (31). Some five years later he began an intensive investigation of this reaction, dealing primarily with the scope of its application (32). It had been proposed that the condensation took place by way of intermediate methylol compounds. However, the work of Bodendorf and Koralewski (33) tended to refute this hypothesis.

Some facts pertinent to this reaction were, for a long time, quite overlooked. As early as 1913, chemists of Bayer and Company had incorporated in the patent literature their observation that methylenediamines could be reacted with ketones to yield β-aminoketones (34). Even prior to that time Knoevenagel had employed methylenediamines to furnish both the formaldehyde and the basic catalyst (amine) necessary for his condensations to produce methylene-bis-malonic esters, subsequently hydrolyzed to prepare glutaric acids (4). Nevertheless, it remained for Lieberman and Wagner (27) to postulate the formation of methylenediamines as Mannich intermediates, and carry out experimental work to support this hypothesis. Further discussion of some of the theoretical aspects will appear in Chapter VII.

As would be expected, many aromatic amines have also been subjected to reaction with formaldehyde (4,9,18,24,35). These will only be mentioned briefly in this work since a large proportion of substances

thus formed exist, at room temperature, as solids rather than liquids. They are, however, generally much more stable than the liquid aliphatic derivatives, due to their solid state as well as to the stabilizing influence of their aromatic substituents.

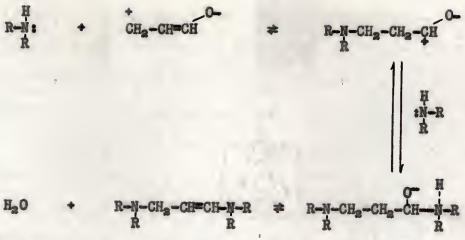
The reaction of aromatic amines with formalin is, however, complicated by the possibility that the methylene group may be formed between the two ring structures as well as between the two nitrogen atoms—i.e., diphenylmethanes, as well as methylenediamines, may result.

ACROLEIN

Consideration of acrolein as a reactant with secondary amines must necessarily involve some appreciation of the resonant system exhibited by this unsaturated aldehyde. The action of its conjugated system may be partially described by the following equation:

$$CH_2{=}CH{-}CH{=}O \quad \rightleftharpoons \quad CH_2{-}CH{=}CH{-}O^{-}$$

Mannich, Handke and Roth (36) found that 1,4-addition occurred in the reactions of acrolein, crotonaldehyde, cinnamic aldehyde, or citral with dimethylamine or piperidine. The resultant materials were diaminopropenes; according to the statements of these investigators, the reaction appeared to proceed somewhat as follows:

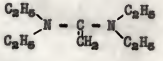


It might be supposed, however, that there would be a small amount of direct attack of the amine on the aldehydic carbon if the following structure contributed to the resonant picture of acrolein to any degree:

Such attack would produce methylenediamines containing a vinyl group attached to the central (methylene) carbon atom. However, no compounds of this type have been prepared and isolated in this reaction.

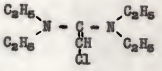
Other methods of synthesis have prepared similar materials — i.e., methylenediamines whose central carbon atom bears unsaturated groupings. However, there are only a few such recorded:

(1) 1,1-Bis(diethylamino)ethylene



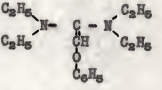
Prepared by the reaction, under pressure, of two moles of diethylamine with one mole of ketene diethylacetal (37).

(2) 1,1-Bis(diethylamino)-2-chloroethylene



Prepared by the vigorous reaction of 1,2-dichloroacetylene with diethylamine (38).

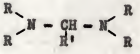
(3) 1,1-Bis(diethylamino)-2-phenoxyethylene



Prepared by the action of the chloro- compound above with sodium phenolate (38).

OTHER MONOFUNCTIONAL ALDEHYDES

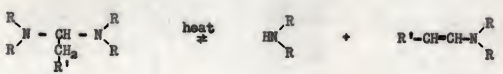
Aldehydes free of interfering resonant systems have been condensed with two moles of various secondary amines to yield methylenediamines containing substituent groups on the central carbon atom. E.g.,



Most of the recorded compounds have been prepared with aromatic aldehydes — these resonant systems do not promote addition at several points, but do increase the activity at the carbonyl carbon. Aldehydes employed have been benzaldehyde, numerous substituted benzaldehydes, α-naphthoic aldehyde, phenylacetaldehyde, phenylpropionaldehyde and furfuraldehyde (5,23, 24,36,39,40,41,42). In almost all cases the products were solid materials.

Likewise, several investigators have proposed the interaction of two moles of secondary amine with one mole of each of several ketones, thereby replacing the carbonyl oxygen with two amino groups (40). The methylenediamines thus formed exhibit two substituents attached to the central, or methylene, carbon atom.

Relatively few aliphatic aldehydes have been employed in this condensation. The reaction of acetaldehyde (23,43), propionaldehyde, butyraldehyde, isobutyraldehyde (41), and chloral hydrate (44) with secondary amines has been recorded. In general, the products obtained are liquids of relatively small stability toward heat, moisture and air. They are purified with considerable difficulty, for, as the temperature required for distillation is applied, they tend to split out a molecule of the original amine, yielding vinyl amines or "enamines" (41):



Even at the temperature of distillation these unsaturated enamines polymerize very readily to produce resins in an exothermic reaction. How-

ever, if the pressure has been suitably reduced before heating, the enamines may be distilled away from the reaction mixture and thus isolated. Enamines thus prepared darken on relatively short exposure to air and light; dilute acids hydrolyze them easily. They have been, in one or two instances, however, hydrogenated to the tertiary amine. In fact, it has been recently proposed that the enamines are the intermediates formed in the course of the Leuckart-Wallach Reaction (45).

Enamines of this type are more or less restricted to the vinyl-type of structure since the nitrogen atom is a tertiary one. However, there are the ketimide-enamine tautomers, such as

(I) (II)

which may exhibit several configurations. Early workers assumed that these materials were imines of structure I (46); later, both chemical (47) and spectrochemical (48) evidence established the fact that the enamine structure (II) was definitely the predominant one.

This type of unsaturated amine is stabilized by conjugation with the carbonyl double bond. Other stabilizing influences have been shown to exist in certain compounds more closely related to the tertiary enamines. For example, the following have been recently recorded in the literature:

(1) $H_2C{=}C(NH{-}C_6H_5){-}CH{=}CH_2$ (49)

(2) $H_2C{=}C(NH_2){-}CH{=}CH_2$ (50)

Enamines prepared by other methods exhibit the same chemical properties (51) as those produced by aldehyde-amine reactions.

AMINO-ACETALS, POTENTIAL AMINO-ALDEHYDES

Amino-acetals are neither new nor novel substances; they have never enjoyed wide use in synthetic organic chemistry, and so have not been extensively investigated. However, the parent compound, amino-acetal, $H_2N{-}CH_2{-}CH(OC_2H_5)_2$, was prepared and characterized by Wohl (52) and Fischer (53) prior to 1900.

Employing the same reaction (the haloacetal with an amino compound) both secondary amino-acetals ($R{-}NH{-}CH_2{-}CH(OR')_2$) (54) and the tertiary derivatives ($R_2N{-}CH_2{-}CH(OR')_2$) (55) have been produced. The piperidine nucleus has been added to the acetal chain (56) and even more complex structures of this type have been recorded (57).

The amino-acetals are generally quite stable; rather strong acid (approximately 20% in some cases) is required to hydrolyze them.

The amino-aldehydes, which the hydrolysis yields, are stable only in solution or as the salt -- the free amino groups react quite readily with the aldehyde groups to give high molecular weight materials.

At least one amino-aldehyde has been prepared other than by the hydrolysis of the amino-acetal. 5-Aminopentanal has been identified as

one of the products of the oxidation of piperidine with hydrogen peroxide (58).

DIALDEHYDES

The literature holds very few data pertaining to the pure di-functional aldehydes--and even less concerning their reaction with amines. This is largely due to the fact that the dialdehydes were obtainable only through great effort and then only in very small quantity, until the recent commercial production of their acetals. One patent has been issued which covers the preparation of high-molecular-weight condensation products from equimolar quantities of dialdehydes and aliphatic primary amines. The polymeric material produced is proposed as useful for rendering textiles water-repellent (59).

AMINO-HALIDES

Although there is much current interest in certain amino-halides ("Nitrogen Mustards") because of their possible therapeutic value (60), these substances have been sought in the past primarily as intermediates in the syntheses of other physiologically-active compounds. A complete coverage of all the literature concerned with their preparation and utilization would by quite extensive.

They have been prepared by the reaction of equimolar quantities of dihalogenated reagents and amines (61), through the scission of the morpholine ring by concentrated hydrobromic acid (62), by hydrolysis of haloalkyl phthalimides (63), by direct chlorination of alkanolamines (64), and by the action of concentrated hydrohalogen acids (65) or phosphorus halides (66) on alkanolamines. However, the most generally-employed

laboratory synthesis is the interaction of thionyl halides and alkanolamines with pyridine to catalyze the low-temperature decomposition of the intermediate sulfite (67). These amino-halides are usually employed as their salts, but the free base may be relatively stable under ordinary conditions (68).

The reaction of amino-halides with aliphatic amines has been of greatest value as a means of preparation of ethylenediamines exhibiting only one alkylated nitrogen atom (i.e., the other nitrogen remains in the form of the primary amino group) (69). Other methods have been used to yield this type of compound, but they were frequently multi-step procedures or required somewhat unusual intermediates (70). Direct alkylation is not very successful for production of the monoalkylated derivatives except when large chains are being introduced (71).

Of almost equal importance to synthetic chemistry, however, has been the use of the amino-halides to introduce the dialkylaminoethyl moiety into more complex amino structures (72) or into the simpler secondary heterocyclic amines (73). Many of the materials thus produced are physiologically active and are of wide application in the field of therapeutics.

Chapter II

THE REACTION OF SECONDARY ALIPHATIC AMINES WITH FORMALDEHYDE

The reaction of secondary aliphatic amines with formaldehyde to produce methylenediamines appears to occur quite readily under a variety of conditions. In this investigation, they have been prepared (a) in aqueous solution with acid catalyst, (b) in aqueous solution with basic catalyst, and (c) in aqueous solution without any catalyst other than the reacting materials themselves.

Many of the compounds synthesized by these methods are not new, but have been prepared in order that careful determination of the unreported physical constants (particularly refractive indices) might be carried out and a calculation of the molar refractions made. All compounds prepared for this phase of the investigation are listed in Table I. Procedure for the synthesis of each new substance listed therein, is given in detail on an individual page following the table.

One new saturated methylenediamine is reported, as well as one new unsaturated compound. Several procedures are employed in attempts to prepare unsymmetrical methylenediamines. The simple member appears to form, but defies purification; the more complex dimethylenetriamine not only forms readily but can be distilled to yield a pure and very stable product—N^1,N^1,N^3,N^3-tetraethyl-N^2-allyldimethylenetriamine.

All attempts to synthesize tetra-iso-propylmethylenediamine were unsuccessful; steric factors seemed to prevent its formation.

Analysis for the percentage of carbon in some of the new com-

pounds is carried out by a modified wet oxidation procedure described at the end of this chapter.

General Procedure

for

Synthesis of Aliphatic Methylenediamines in Aqueous Solution

(1) With acid catalyst.

In a 200 ml., three-necked, round-bottomed flask, equipped with a mechanical stirrer, reflux condenser, and thermometer, place 0.6 moles of the secondary aliphatic amine. To this add a solution of 4 ml. (0.048 moles) of concentrated hydrochloric acid in 30 ml. of water.

With stirring, introduce 0.3 moles of formaldehyde (37-40% aqueous solution) at such a rate that the temperature of the reaction mixture rises to about 60° C. and is there maintained. After all is added continue stirring for two hours; then allow the mixture to stand for 24 hours at room temperature.

With cooling, add solid Na_2CO_3 (KOH or NaOH may be used but it is more difficult to control the evolution of heat) until the product separates as an oily layer. Separate the non-aqueous material; extract the alkaline aqueous solution with several small portions of benzene. Combine the extracts with the previously-separated upper layer and dry briefly over solid KOH. Fractionate through a simple packed column, removing the last traces of water as the benzene-water azeotrope; careful refractionation of the product will be required for exact values of the physical constants.

(2) With basic catalyst.

This operation is carried out in a manner identical to that with the acid catalyst, except that approximately 0.05 moles of $Ba(OH)_2$ or NaOH

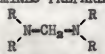
is substituted for the hydrochloric acid.

(3) Without added catalyst.

The same procedure is again repeated, except that neither hydrochloric acid nor any of the alkali bases are added.

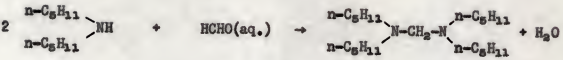
TABLE I

COMPARATIVE TABULATION OF PHYSICAL CONSTANTS
OF METHYLENEDIAMINES PREPARED FOR THIS STUDY



-methylenediamine Empirical formula Molecular weight	Boiling Point °C.	Mm.	d	n	MR_D Obs.	MR_D Calcd. (V)	Dev.	Ref. (A This Study)
Tetramethyl-	85		$^{16.7}_{4}$ 0.7491					(6)
	80-83							(6)
$C_5H_{14}N_2$	85							(9)
102.18	82.0-83.2		$^{25}_{4}$ 0.7440	$^{25}_{D}$ 1.3984	33.175	32.747	+0.428	A
Tetraethyl-	168		$^{18}_{0}$.8105					(6)
	168							(4)
$C_9H_{22}N_2$	166-9	760.7						(3)
158.28	62.3	19	$^{25}_{4}$ 0.7843	$^{25}_{D}$ 1.4233	51.420	51.335	+0.085	A
Tetra-n-propyl-	225-30		$^{18}_{0}$.8014					(6)
	215-25							(5)
$C_{13}H_{30}N_2$	115	15						(9)
214.39	98.5-99.5	9.2	$^{25}_{4}$ 0.7974	$^{25}_{D}$ 1.4333	69.923	69.995	-0.072	A
Tetra-n-butyl-	112-14	3		$^{20}_{D}$ 1.4437				(7)
	252-4	760						(29)
$C_{17}H_{38}N_2$	163	21						(29)
270.49	107.8-109.0	1.5	$^{25}_{4}$ 0.8068	$^{25}_{D}$ 1.4407	88.478	88.475	+0.003	A
Tetra-iso-butyl-	245-55							(5)
$C_{17}H_{38}N_2$								
270.49	91.8-93.3	1.5	$^{25}_{4}$ 0.8018	$^{25}_{D}$ 1.4380	88.560	88.615	-0.055	A
Tetra-n-amyl-								
$C_{21}H_{46}N_2$			$^{21}_{4}$ 0.8130	$^{21}_{D}$ 1.4458	107.09	107.14	-0.05	A
326.59	75-78	1						
Tetraallyl-								
$C_{13}H_{22}N_2$			$^{25}_{4}$ 0.8411	$^{25}_{D}$ 1.4662	67.961	68.215	-0.254	A
206.32	80.0-80.2	4.2						

Synthesis of Tetra-n-amylmethylenediamine



In a 200 ml., three-necked, round-bottomed flask, equipped with a stirrer and reflux condenser, place 48.1 g. (0.3 moles) of di-n-amylamine. Warm to 60-70° and pour in 4.6 g. (0.15 moles; 12.4 g. of 37% aq. soln.) of formaldehyde, all at once.

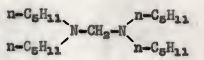
Heat to reflux with stirring; maintain gentle heating for 2 hours. Then allow the mixture to cool and stand overnight.

Add 25 g. of flake KOH with cooling; separate the non-aqueous layer and extract the aqueous layer with 20 ml. of benzene. Combine the extracts and non-aqueous portions, dry briefly over KOH and fractionate. The last traces of water will be removed as the benzene-water azeotrope.

Collect the fraction boiling at 70-78° at 1 mm.. Since there is considerable forerun of unreacted amine, the yield is only 22 g., which is 44% of the theoretical, based upon the original amount of amine used.

Refractionation of the product from several runs gives the material with constants as listed on the following page.

TETRA-n-AMYLMETHYLENEDIAMINE



Empirical Formula ..... $C_{21}H_{46}N_2$

Molecular Weight 326.59

Boiling Point ..... 75-78° at 1 mm.

D^{21}_{21} 0.8146

D^{21}_{4} 0.8130

n^{21}_{D} 1.4458

Mr_D :

Calcd. 107.06 (E) ; Found 107.09 ; Deviation +0.03 (E)

107.14 (V) -0.05 (V)

Appearance:

Colorless to light yellow, slight ammoniacal odor.

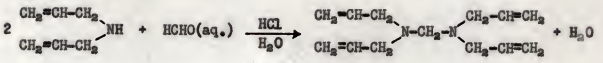
Solubility:

Soluble in common organic solvents; insoluble in water.

Analysis: (Modified wet oxidation)

%C : Calcd. 77.23; Found 76.81; Deviation 5.5|1000 parts.

Synthesis of Tetraallylmethylenediamine

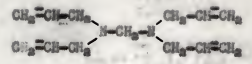


In a 200 ml., three-necked, round-bottomed flask, equipped with a mechanical stirrer, reflux condenser, and thermometer, place 47.2 g. (0.485 moles) of diallylamine (b. 110-111). To this add a solution of 4 ml. (0.048 moles) of concentrated hydrochloric acid in 30 ml. of water.

With stirring, introduce 7.3 g. (0.243 moles; 19.6 g. of 37-40% aqueous solution) of HCHO at such a rate that the temperature of the reaction mixture rises to 65° C. and is maintained at that point. After all of the solution has been added, stir for an additional hour, then allow the mixture to stand overnight at room temperature.

With cooling, add solid Na_2CO_3 until an oily layer separates. Remove this layer; extract the aqueous solution with two 15-ml. portions of benzene. Combine the extracts with the oily material and dry for just a few minutes over solid KOH. Decant the liquid from the solid base and fractionate through a 5-10 plate column. The benzene-water azeotrope completely removes the last traces of water from the product, which is collected (38 g.) from 80-86° at 4.3 mm. The crude yield thus prepared is 76% of the theoretical, based on the original amount of amine used. Refractionation gives the pure compound with properties as recorded on the following page.

TETRAALLYLMETHYLENEDIAMINE



Empirical Formula .....$C_{13}H_{22}N_2$

Molecular Weight..... 206.32

Boiling Point..... 80.0-80.2° at 4.2 mm.

D_{20}^{20}.....0.8426

D_4^{20} 0.8311

n_D^{20} 1.4662

Mr_D :

Calcd. 68.246 (E) ; Found 67.961 ; Deviation -0.285 (E)

68.215 (V) -0.254 (V)

Appearance :

Colorless, mobile liquid with sharp ammoniacal odor.

Solubility :

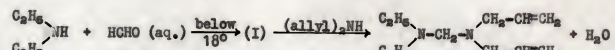
Soluble in common organic solvents; only very slightly soluble in water.

Analysis : (By means of modified wet oxidation)

%C : Calcd. 75.67; Found 75.22; Deviation 6/1000 parts.

Attempted Synthesis of Diethyl-diallylmethylenediamine

METHOD A



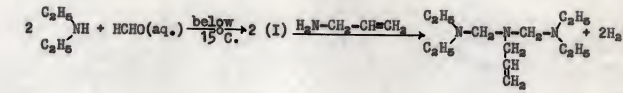
Mix 20.5 ml. (14.6 g.; 0.2 moles) diethylamine with 15 ml. of water in a 200 ml., three-necked, round-bottomed flask, and cool to below 18°. With stirring, add 6.05 g. (0.2 moles; 16.1 g. of 37% aq. solution) of HCHO at such a rate that the temperature does not rise above 18°. Stir for 20-30 minutes at this temperature; then, introduce 19.4 g. (0.2 moles) of diallylamine, allowing the temperature to rise to 35°, but no higher. When all added, stir for another 30 minutes; allow to stand overnight. Separate the non-aqueous layer, dry, and fractionate.

Distillation yields both the tetraethyl- and the tetraallyl-methylenediamines; further, there is also collected a small fraction, about five grams, boiling at 85-95° | 30 mm. This latter appears to be the unsymmetrical amine, but attempts to purify it only bring about disproportionation. Redistillation yields only a little more of the tetraethyl- derivative and the slightest quantity of material boiling higher than the originally-collected sample.

METHOD B

The exchange reaction, illustrated in the equation, seemed to proceed quantitatively when equimolar portions of the tetraethylmethylenediamine and diallylamine were gently refluxed. The theoretical amount of the lower-boiling diethylamine could be readily removed; but as the temperature rose, tetraethyl- and tetraallyl- fractions were again collected, as well as a small amount of the 85-95°/30 mm. intermediate cut. However, no pure product was capable of isolation by distillation, as disproportionation again appeared to occur.

Synthesis of N^1,N^1,N^3,N^3-Tetraethyl-N^3-allyldimethylenetriamine



In a 500 ml., three-necked, round-bottomed flask, equipped with a mechanical stirrer, dropping funnel, and thermometer, place 26.9 g. (0.9 moles; 71.8 g. of 37% aq. solution) of HCHO. Cool to below 15° C. To this add, dropwise, with stirring, 90.6 ml. (64.5 g.; 0.88 moles) of diethylamine at such a rate that the temperature may be maintained below 15° by means of cooling with an ice bath. After all is added, stir at this temperature for an additional 0.5 hours; then, with continued stirring, remove the cooling and allow the mixture to come to room temperature.

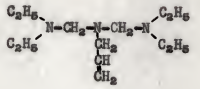
At room temperature, add 33 ml. (25 g.; 0.44 moles) of allylamine very slowly with stirring. Maintain agitation for another hour after addition is complete and allow the mixture to stand overnight.

Cool and pour into a cooled solution of 100 g. KOH in 100 ml. of water. Separate the non-aqueous layer which forms; extract the alkaline aqueous layer with two 30 ml. portions of ether. Combine the extracts with the oily material and dry over solid KOH. Fractionate using a 5-10 plate column. Twenty grams of product, boiling at 81-86° at 1.2 mm. is collected. This crude yield represents 20% of the theoretical amount, based on the original amount of either amine.

Successive syntheses gave yields of no greater than 25%, even with numerous variations in procedure. This, of course, was due to the

concurrent formation of considerable amounts of the tetraethylmethylenediamine. Combined yields were carefully refractionated to give the pure compound with the constants recorded on the following page.

N^1,N^1,N^3,N^3-TETRAETHYL-N^2-ALLYLDIMETHYLENETRIAMINE



Empirical Formula	$C_{13}H_{29}N_3$
Molecular Weight	227.39
Boiling Point	85-86.5° at 1.4 mm.
D_{20}^{25}	0.9189
D_4^{25}	0.9173
n_D^{25}	1.4863

Mr_D :

Calcd. 73.587 (E) ; Found 71.210 ; Deviation -2.377 (E)

73.246 (V) -2.036 (V)

Appearance:

Colorless, almost odorless, liquid, turning slightly yellow on standing.

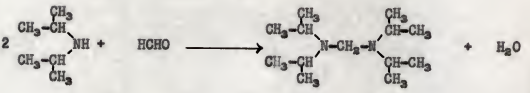
Solubility:

Soluble in common organic solvents; insoluble in water.

Analysis: (By means of modified wet oxidation)

%C : Calcd. 68.66; Found 68.46; Deviation 2.9|1000 parts.

Attempted Synthesis of Tetra-iso-propylmethylenediamine



METHOD A

Many attempts were made to synthesize this compound in aqueous solution. Almost all possible modifications of the general procedure were carried out without success. Steric factors may have something to do with the inability to prepare this methylenediamine.

METHOD B

This synthesis was also attempted in relatively anhydrous medium, using methanolic formaldehyde with potassium carbonate for the condensing agent. This procedure was no more successful than the others, but it was carried out as follows:

In a 250-ml. Erlenmeyer flask place 65.5 ml. (47.2 g.; 0.47 moles) of di-iso-propylamine, 20 g. (0.145 moles) of powdered, anhydrous K_2CO_3, and 7.05 g. (0.23 moles; 17.6 g. of 40% methanolic solution) of HCHO. Stopper the flask loosely and allow it to stand for 10 days at room temperature with occasional shaking. A reaction of some sort occurs, for the carbonate seems to pick up moisture and become somewhat slushy.

At the end of this period, filter and fractionate. After the methanol is removed, a cut is taken around 70° which appears to contain the unreacted amine. Another sizeable portion is collected at 50-55°|30 mm.;

this seems to be the methoxy-amino compound, but continued reflux with further quantities of the amine still fails to replace the methoxy radical and form the desired methylenediamine. A polymeric material is the only higher-boiling product remaining in the flask.

Modified Wet Oxidation Analysis for Carbon In the Presence of Amino Nitrogen

Analysis for the carbon content of these nitrogenous materials is carried out with excellent accuracy using a slight modification of the wet combustion procedure of Pollard and Forsee (74).

The absorption train is assembled so that the gases produced by the oxidation must pass first through saturated silver sulfate solution (two tubes), then into a drying tube filled with concentrated sulfuric acid, out over glass wool and into the weighed ascarite tube where the carbon dioxide is absorbed.

The exit end of the absorption tube is protected with a safety tube containing both ascarite and calcium chloride.

A sample of approximately 100 mg. of the material to be analyzed is placed in the oxidizing flask, along with the dry reagents (4 g. powdered potassium dichromate and 1 g. of potassium iodate). The flask is attached to the train and carbon dioxide-free air is drawn through the system for one hour by means of gentle suction applied at the safety tube (an aspirator or mariotte bottle may be used). At the end of this time, the inlet to the system is closed, the absorption tube carefully weighed and returned to the train. The liquid reagents (a mixture of 10 ml. of concentrated sulfuric acid and 10 ml. of 85% phosphoric acid) are then carefully and slowly admitted to the oxidizing flask through the side-inlet tube placed there for that purpose.

When the first reaction abates, heat is applied to the bottom of the flask with a micro burner. A steady evolution of gas is maintained,

by the gradual increase in amount of heating, until bubbles cease to pass through the system. (Total time of heating is usually 1-1.25 hours.)

Gentle suction is again applied at the safety tube, the carbon dioxide-free air inlet is opened and heating is discontinued. While the system cools, it is again swept for one hour.

At the end of this period, the absorption tube is weighed and the percent of carbon calculated.

This procedure requires a minimum amount of the operator's attention, while allowing an excellent quantitative determination. When the reagents are used as here prescribed, no other steps will ordinarily be necessary for removal of the oxides of nitrogen formed in the combustion. Other methods attempt to remove the nitrogen oxides from the system prior to the carbon dioxide absorption (75), for the purpose of measuring them as well. Application of the proper mathematical factor to the weight of the nitrogen-containing gases will allow calculation of the percent nitrogen as well as the percent of carbon.

The analytical method here employed is, however, outstanding for its ease of operation and ability to utilize small samples, as well as the simplicity of the equipment required.

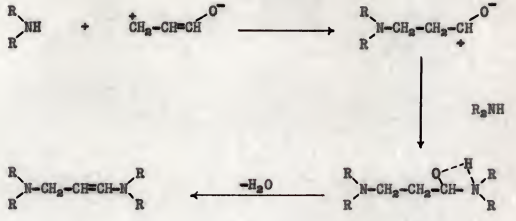
Chapter III

THE REACTION OF SECONDARY ALIPHATIC AMINES WITH ACROLEIN

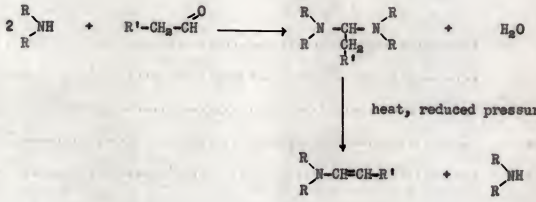
The first reactions of secondary amines with acrolein, in the course of this investigation, were conducted with the hope that the structure, $CH_2{=}CH{-}\overset{+}{C}H{-}O^-$, might contribute appreciably to the resonant picture of this aldehyde. Attack of the amino group at this positive center would yield methylenediamines with vinyl groupings attached to the central carbon atom.

However, only the type of addition previously reported by Mannich, Handke and Roth (36) was found to occur in quantity sufficient to isolate any yield of product therefrom. Two new propenediamines were thus prepared and characterized.

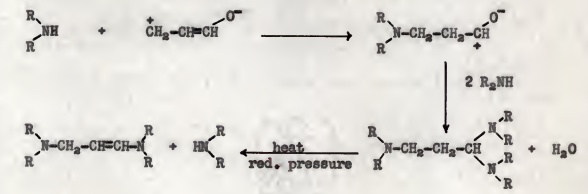
In the reference cited, Mannich and coworkers propose that the carbon-to-carbon double bond of these propenediamines is produced by "splitting-out of water". On the basis of this statement, the course of the reaction could be outlined as follows:



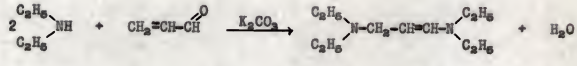
However, in a concurrent publication (41) Mannich and Davidsen suggest that the formation of the enamines occurs by the "splitting-out" of one mole of amine from methylenediamines to form the carbon-to-carbon double bond; e. g.



Since these two reactions are almost identical, it is natural to suppose that decomposition of the methylenediamine might also play a large part in the preparation of the propenediamines. Actually both water and amine may be eliminated, and both mechanisms may be necessary to describe the course of the reaction completely. Observations of the syntheses, as conducted in this research, suggest that a large portion of the products are formed according to the following scheme:



Synthesis of N,N,N',N'-Tetraethylpropenediamine-1,3



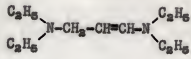
In a three-necked, round-bottomed flask, equipped with a mechanical stirrer, thermometer, and dropping funnel, place 33.5 ml. (23.8 g.; 0.325 moles) of diethylamine and 30 ml. of diethyl ether. To this add dropwise, with stirring, a solution of 11 ml. (9.1 g.; 0.16 moles) of acrolein, dissolved in 15 ml. of ether, at such a rate that the temperature does not rise above 10° C. (Use ice cooling.) During the addition, introduce 10 g. of anhydrous, powdered K_2CO_3 in small portions. (Time of addition -- 15 to 20 minutes.)

Stir the mixture at 5-10° for an additional hour. Then filter, remove the solvent with water-aspirator vacuum, and fractionate as rapidly as possible under reduced pressure.

Distillation is most readily carried out from a Claisen flask; however, the flask must be packed with glass wool to prevent violent bumping. Distillation through a 20-inch, packed and heated column gives a purer product without requiring the use of the glass wool. In either case, however, the yield from the distillation is only equal to about 50% of the crude product, due to the thermally-induced formation of resins and high-boiling polymers.

Combination of the yields from several runs and refractionation through the 20-inch packed column (with the repeated 50% loss due to polymerization)gives the compound with the physical properties recorded on the following page.

N,N,N',N'-TETRAETHYLPROPENEDIAMINE-1,3



Empirical Formula	$C_{11}H_{24}N_2$
Molecular Weight	184.32
Boiling Point	51-53 at 0.5 mm.
D_{25}^{25}	0.8290
n_D^{25}	1.4627

Mr_D :

Not calculated for this series of compounds. Exposed to the air they polymerize rapidly. The thin film that is placed on the lens of the refractometer thickens at such a rate that the refractive index decreases 0.0002 units every five seconds.

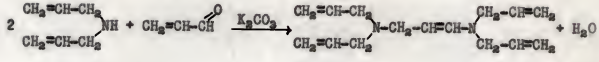
Appearance:

A colorless liquid only at the moment of distillation. A trace of yellow coloring appears even in the short time required to remove an 8 ml. sample. However, a sample sealed in a highly-evacuated ampoule has remained at an almost constant shade of light brown, and at original mobility, for a period of two years, even though exposed to indirect sunlight.

Solubility:

Soluble in common organic solvents; insoluble in water.

Synthesis of N,N,N',N'-Tetraallylpropenediamine-1,3



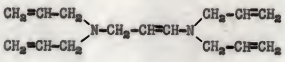
In a 200-ml. three-necked, round-bottomed flask, equipped with a mechanical stirrer, dropping funnel, and thermometer, place 25.1 g. (0.258 moles) of diallylamine and 75 ml. of diethyl ether. Cool to -5° C. in an acetone-dry ice bath.

Add dropwise, with stirring, a solution of 8.6 ml. (7.25 g.; 0.13 moles) of acrolein in 20 ml. of ether at such a rate that the temperature does not rise above 0° C. During the course of the addition, introduce 15 g. (0.14 moles) of powdered, anhydrous Na_2CO_3 in small portions.

When addition is completed, allow temperature to rise in the range of 0-10° and continue stirring for 0.5 hrs. Filter, removing solvent with water-aspirator vacuum. (Use no heating at this point.)

Fractionate at once from a Claisen Flask (packed with glass wool), collecting the fraction boiling from 88-92° at 0.5 mm. The yield is 6 g., which is 20% of the theoretical amount, based on the original amount of the amine used. There is a large amount of resin formed in the distilling flask.

N,N,N',N'-TETRAALLYLPROPENEDIAMINE-1,3



Empirical Formula	$C_{18}H_{24}N_2$
Molecular Weight	232.258
Boiling Point	88-92 at 0.5 mm.
D_{25}^{25}	0.8811
n_D^{25}	1.5052

Mr_D :

Not calculated for this series of compounds.

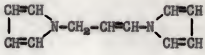
Appearance:

Colorless liquid only at the moment of distillation. A sample bottled at atmospheric pressure darkened and thickened to a syrup within approximately 8 hours.

Solubility:

Soluble in common organic solvents; insoluble in water.

Attempted Synthesis of 1,3-Dipyrrolopropene

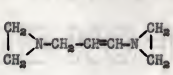


All efforts to prepare this compound, following the general procedures previously outlined, produced only resins which dried into hard films or cakes in the presence of air at room temperature.

The actual preparation reaction seemed to proceed smoothly at the lowered temperatures employed; but, on removal of the solvent, polymerization occurred so rapidly that distillation, even though performed at once and at low pressures, was impossible.

The polymers produced were very viscous syrups that dissolved rather readily in 95% ethanol, but darkened somewhat on standing. The solutions of polymer were readily absorbed by paper surfaces, forming flexible, waterproof, tear-resistant materials. These materials, however, darkened more with time and became somewhat less flexible than at first.

Attempted Synthesis of 1,3-Diethyleniminopropene



All attempted syntheses of this compound formed resins even at -5° C., in an inert solvent, and in the absence of acid catalysts. The polymers produced were similar to those described above.

Chapter IV

THE REACTION OF SECONDARY ALIPHATIC AMINES WITH OTHER MONO-ALDEHYDES

Aliphatic aldehydes other than formaldehyde were also reacted with secondary amines to demonstrate the production of carbon-substituted methylenediamines. Only a few compounds of this type have been reported; those are reviewed in Chapter I.

It was found that the initial temperature of the reaction must be maintained at about 5°; in all syntheses where it was allowed to rise in the early stages, resins were the only products formed. Further, it was determined that the water formed in the reaction must be removed as rapidly as possible; this was accomplished by use of anhydrous K_2CO_3 as the absorbing agent, as well as the condensing agent. All acid catalysts gave polymeric products.

Another basic catalyst, $NaNH_2$, was examined for use in this synthesis. It appeared to bring about a more rapid reaction than K_2CO_3, evolving ammonia readily, but the reagent, or the resultant NaOH, formed a thick, slushy complex with either the reactants or products; resolution of the mixture with water hydrolyzed whatever product might have been formed, returning it to the original amine.

One new compound was prepared and its constants recorded on the following pages. These materials are relatively stable at room temperature, although their color deepens considerably on standing. However, all distillations involving these compounds must be carried out with the greatest care and at the lowest practicable pressures. Rising temperature causes one mole of amine to split out, giving rise to readily-polymerizable enamines or vinyl amines.

Synthesis of 1,1-Bis(di-n-butylamino)propane

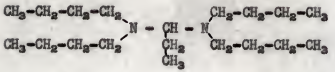
In a 200 ml., round-bottomed, three-necked flask, equipped with a mechanical stirrer and dropping funnel, place 113 ml. (86.5 g.; 0.67 moles) of di-n-butylamine (b. 159-60°) and 20 g. anhydrous, powdered K_2CO_3. Cool to 0-5°.

Add dropwise, with stirring, 24.2 ml. (19.5 g.; 0.33 moles) of redistilled propionaldehyde (b. 48.8-50.3) maintaining temperature below 5°. When all added (about 0.5 hrs.), stir for an additional two hours while the mixture comes to room temperature. Then, allow to stand for two weeks. Agitate the mixture occasionally during this period and replace the K_2CO_3 once or twice.

Remove the solid condensing agent, and distill off the unreacted di-n-butylamine under water-pump vacuum. There remains about 40 g. of crude product.

The first distillation of this material through a packed column yields some low-boiling substances, about 20 g. of purer material boiling at 69-96° at 4.2 mm., and some polymeric residue. Redistillation through an efficient column gives 8 g. of pure product boiling from 75.2-79.0 at 2.4 mm.; physical properties are recorded on the following page.

1,1-Bis(DI-n-BUTYLAMINO)PROPANE



Empirical Formula	$C_{19}H_{42}N_2$
Molecular Weight	298.54
Boiling Point	75.2-79.0° at 2.4 mm.
D_{25}^{25}	0.8211
D_4^{26}	0.8187
n_D^{25}	1.4423

Mr_D :

Calcd. 97.822 (E) ; Found 96.545 ; Deviation -1.277 (E)

97.747 (V) -1.202 (V)

Appearance:

Light yellow, oily liquid; penetrating odor(hydrolysis in air).

Solubility:

Soluble in common organic solvents; insoluble in water.

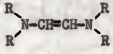
Analysis: (In aqueous alcohol--mixed indicator)

Neutral equivalent 301.

Chapter V

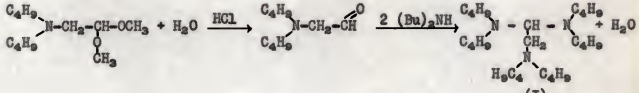
THE ATTEMPTED SYNTHESIS OF DIAMINOETHENES

Since it was apparent that double bonds could be introduced by the formation of methylenediamine structures, with the subsequent splitting-out of one mole of amine, it was proposed that this reaction might be utilized to produce diaminoethenes:

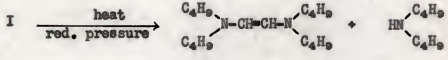


Amines of this type had never been reported.

Dibutylaminodimethylacetal was prepared by lengthy reflux of the secondary amine with chlorodimethylacetal (55). It was planned to hydrolyze the acetal to give the amino-aldehyde in solution. This would then be reacted with an additional two moles of the original, or another, amine to produce the substituted methylenediamine. Careful decomposition of this intermediate by the splitting-out of one mole of the amine would yield the diaminoethene:



(I)



Numerous attempts were made to follow this scheme, but all returned the unreacted starting materials, or produced viscous, resinous substances. The primary difficulty lay in the fact that the amino-acetal could only be hydrolyzed to the amino-aldehyde in aqueous acid solution; the subsequent condensation with the amine could only be carried out successfully in relatively anhydrous basic medium.

Chapter VI

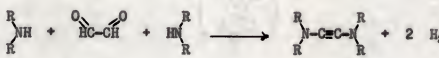
THE ATTEMPTED REACTION OF SECONDARY ALIPHATIC AMINES WITH ALIPHATIC DIALDEHYDES

If the reaction of secondary amines with monoaldehydes may be used to prepare compounds which exhibit mono-unsaturation (enamines), it is to be expected that the same reaction applied to the dialdehyde molecule could produce di-unsaturation.

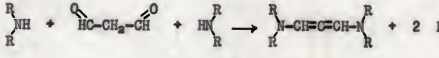
Further examination of the possible course of this reaction reveals that three completely new types of unsaturated amines might be synthesized simply by reaction with the three available dialdehydes.

Glyoxal, the simplest dialdehyde, has been marketed in aqueous solution for some years; however, it has not been until recently that malonic aldehyde (as 1,1,3,3-tetraethoxypropane) and succinic aldehyde (as the cyclic acetal, 2,5-diethoxytetrahydrofuran) have also become available. Under proper conditions, the following reactions should be possible:

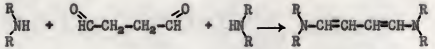
(1) Glyoxal



(2) Malonic aldehyde



(3) Succinic aldehyde



Since the acetals may only be readily hydrolyzed to the free aldehyde in the presence of hydrogen ion, the first attempts to bring about the condensations (depicted above) were carried out in acid solution. This definitely was not the proper way to effect the desired condensation; all variations of the acidic process produced only resins. The results were the same with diethylamine, dibutylamine, or piperidine.

There was one exception, however. Monophenylpiperazine did yield a solid in reaction with succinic aldehyde. This product was recrystallized one time from butanol, but a second recrystallization was not successful — the material changed form, becoming plastic and insoluble in the solvent. Analyses of the once-recrystallized material showed no constant value for the percent of nitrogen -- figures ranged from 14 to 18%.

The next phase of this investigation would be to explore the possibility of releasing the aldehyde in a minimum quantity of dilute acid solution. This solution would be added to an excess of the amine in the presence of powdered, anhydrous K_2CO_3. Very careful temperature control would be necessary; the reaction temperature should be maintained at less than 5°. It is believed that under these conditions the reaction would take place smoothly; the isolation and purification of the product would still be a big problem in any medium.

Chapter VII

METHYLENEDIAMINES -- A THEORETICAL DISCUSSION

To the synthetic organic chemist, the molar refraction may be a valuable tool. From two physical measurements (density and refractive index) he may calculate a figure which, should it be in close agreement with the sum of the atomic refractions of the component atoms of the synthesized molecule, may indicate additional proof of the proposed structure.

There are several limitations to the use of this aid. In the first place, the material examined must be quite pure in order to afford physical constants of reasonable accuracy; secondly, the recorded values of atomic refraction (76,77) actually apply with great accuracy only to the specific series of compounds for which they are determined. Slight alteration in the electronic configuration around a specific component atom, as would be obtained by placing it in a molecule having structure different from that in which the value of the atomic refraction was observed and determined, may produce such a deviation that the calculated and observed molar refractions will be far from agreement.

Deviation in Mr_D values should not be greater than 0.1 unit, if they are to be of real value in proof of structure.

It will be observed that many of the compounds prepared and reported in this investigation show considerable deviation of the observed molar refraction from that calculated. In most cases, the observed value is less than the calculated one.

One of the first compounds prepared for this study (tetraallylmethylenediamine) showed such a lowering that there was considerable con-

cern as to whether the desired material had actually been prepared. However, very careful re-purification and re-determination of constants failed to change materially the values already recorded; analytical data completely supported the proposed structure, as did the method of synthesis. Still, the molar refraction was 0.254 units low.

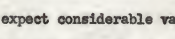
Other saturated members of the methylenediamine series were then prepared to see whether they too showed this same kind of deviation. It was found that the first of the series, tetramethylmethylenediamine, exhibited an exaltation; succeeding members approached the expected values. The comparative data are listed in Table II.

The large positive deviation exhibited by the tetramethyl derivative might indicate that the presence of the four methyl groups introduces some special effect; however, a definite statement may not be made for there is some doubt as to the validity of the physical constants determined and recorded for this compound, even though more than ordinary care was employed in their determination. This material is so readily hydrolyzed by atmospheric moisture that the odor of formaldehyde arising from it is always very strong. Unless absolutely anhydrous conditions could somehow be maintained for the distillation and subsequent evaluation of the constants, there cannot be real dependence on the values obtained.

The tetraethyl derivative, however, also shows an observed Mr_D value greater than that calculated (a positive deviation of 0.085 units). This disagreement of values is not great enough to cause any concern as to the structure of the compound, but it is large enough to substantiate the direction of deviation of the tetramethyl homologue.

The configuration of the valence electrons of the component

nitrogen atoms is probably somewhat modified by attachment of both nitrogens to the same carbon atom:



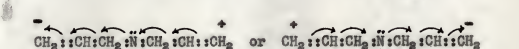
Since the nitrogen atom, according to Pauling (78), exhibits a relative electronegativity of 3.0, while the carbon atom can only muster a value of 2.5, it is logical to expect considerable variation in the electron arrangement as less electronegative groups are substituted onto the competing nitrogens.

It was originally hoped that there might be a uniform deviation applicable to this whole series of compounds. Experimentation proved that this was not the case—the first members showed an exalted value, while the succeeding ones with the larger alkyl substituents tended to approach the calculated values very closely. The unsaturated allyl radicals dropped the figure 0.254 units below that calculated. The more complex, allyl-substituted dimethylenetriamine (see page 28) introduced a multiplicity of effects and demonstrated a negative deviation of 2.036 units.

These observations are entirely in agreement with the proposal that the variation of the relative electronegativity of the substituting chains is going to vary considerably the effect on the whole electronic configuration of compounds such as the methylenediamines.

Further illustration of this effect may be shown in an entirely different series of compounds — the ethylenediamines described in Chapter VIII which follows. These materials would be expected to behave more normally; however, the depression of the observed value is even of greater magnitude than that shown by the methylenediamines. But, in this

case, it is proposed that the deviation is due to the fact that two allyl groups are attached to a single nitrogen atom in each of the compounds of the series. These two unsaturated groups seem to exert considerable influence on the nitrogen's unshared pair of electrons:



It will be noted from Table III, listing the deviations of the ethylenediamine series, that the presence of four allyl groups on the molecule (tetraallylethylenediamine) brings about a depression of 0.414 units; two allyl groups show only about half as much effect, but accurate calculation cannot be made because of the ring structures on the other ends of the molecules. These exert modifying influences which are not accurately recorded.

The value used for the allyl radical is the best available, having been determined specifically by Vogel (77) to include the effect of unsaturation; however, this measurement was not made on a series of compounds of this type.

Turning attention again to the methylenediamines, it should be pointed out that no study of these substances would be complete without mention of structural and behavioral similarities between them and the familiar acetals. These diamines not only show the structural analogies usually drawn between the nitrogen and oxygen systems but also show similarities in chemical activity — both are stable in basic solution but hydrolyze under acidic conditions; both can be used in certain reactions to act as a source of supply of the original reagents used in

TABLE II

METHYLENEDIAMINES; OBSERVED AND CALCULATED MOLAR REFRACTIONS

-methylenediamine	Calcd. Mr_D (V)	Obs. Mr_D	Deviation
Tetramethyl-	32.747	33.175	+0.428
Tetraethyl-	51.335	51.420	+0.085
Tetra-n-propyl-	69.995	69.923	-0.072
Tetra-n-butyl-	88.475	88.478	+0.003
Tetra-iso-butyl-	88.615	88.560	-0.055
Tetra-n-amyl-	107.14	107.09	-0.05
Tetraallyl-	68.215	67.961	-0.254

TABLE III

ETHYLENEDIAMINES; OBSERVED AND CALCULATED MOLAR REFRACTIONS

Compound	Calcd. Mr_D (V)	Obs. Mr_D	Deviation
Tetraallyl-ethylenediamine	72.862	72.450	-0.414
Diallyl-diethyl-ethylenediamine	64.422	64.365	-0.057
N-(Diallylaminoethyl)-piperidine	67.057	66.856	-0.201
N-(Diallylaminoethyl)-pyrrolidine	62.410	62.264	-0.146

their preparation.

A search of the literature shows that this observation had been made some time prior to our recognition of these facts. As early as 1928 Strain proposed that certain aromatic Schiff bases might be considered as "ammono aldehyde acetals" (79). Feldman and Wagner (80) in 1942 clearly set forth the concept as follows:

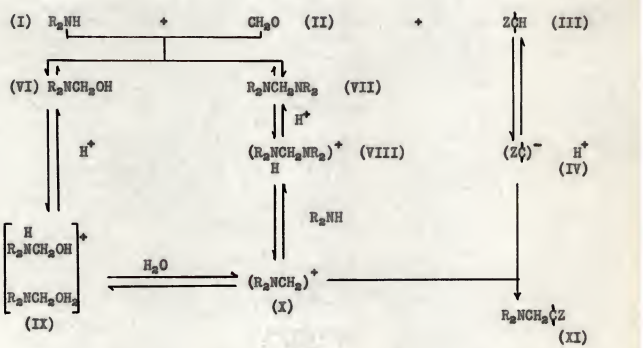
	Ammonia System		Water System
$H_2N-CH_2-NH_2$	Diaminomethane, known in the form of derivatives.	$HO-CH_2-OH$	Formaldehyde hydrate
$RNH-CH_2-NHR$	Methylenediamines from primary amines.		
$R_2N-CH_2-NR_2$	Methylenediamines from secondary amines including those from cyclic sec. amines; e.g., piperidine	$RO-CH_2-OR$	Formaldehyde acetals

The fact that the reaction of two molecules of secondary amine with formaldehyde (to yield methylenediamines) is actually a Mannich Reaction raises the possibility that careful study might throw some light onto the course thereof.

The most careful work on the mechanism of this reaction prior to 1949 was that of Bodendorf and Koralewski (33), who attempted to prove that the methylol compounds of neither the amine nor the ketone were the real intermediates for this reaction. They based their conclusions primarily on the fact that the yield of the Mannich base was less when the

methylol compounds were used as the starting materials, than when the amine and formaldehyde were employed. Thus, they reasoned that the formation of the methylol was merely a side-reaction that occurred in conjunction with the desired condensation.

Results of this investigation of the reactions of the methylenediamines suggest that a carbonium ion might be the actual intermediate in the Mannich reaction. This observation is recorded as of April 21, 1949. But this was too late, for Lieberman and Wagner had been carrying out similar research and in a short time published their excellent paper on the "Course of The Mannich Reaction" (27). Therein they use the following diagram to describe fully their concept of the reaction:



Preliminary investigations, abandoned following appearance of this publication, support this work completely. It seems, however, that more emphasis should be placed on the carbonium ion as the true Mannich

intermediate. The chemical nature of the methylenediamines is such that they may readily decompose to supply this ion for the reaction — or may exist, to a considerable extent, in this state at all times. Support for this concept of rather unusual structure is lent not only by this study of molar refraction but also by the work of Stewart and Aston (14) on the base strength of tetraethylmethylenediamine and the related compounds of the following structure:

These workers conclude, on the basis of the basic ionization constants determined, that these materials may be either amphoteric or tautomeric substances.

Chapter VIII

THE PREPARATION OF AMINO-HALIDES; THEIR REACTION WITH SECONDARY AMINES TO YIELD UNSATURATED ETHYLENEDIAMINES.

Substituted ethylenediamines had been prepared by the interaction of amino-halides and amines. It was proposed that allyl groups could be introduced by this method; toward this end, preliminary investigations were begun with N,N-bis(β-chloroethyl)allylamine:

$$Cl\text{-}CH_2\text{-}CH_2\text{-}N(CH_2\text{-}CH{=}CH_2)\text{-}CH_2\text{-}CH_2\text{-}Cl$$

The preparation of small quantities of this compound was recorded by Ford-Moore, et al (81); slight modification of this procedure afforded the production, in two steps, of larger quantities:

(1) $2\ HN(CH_2\text{-}CH_2\text{-}OH)_2 + Br\text{-}CH_2\text{-}CH{=}CH_2 \Rightarrow N(CH_2\text{-}CH_2\text{-}OH)_2\text{-}CH_2\text{-}CH{=}CH_2 + HN(CH_2\text{-}CH_2\text{-}OH)_2 \cdot HBr$

(I)

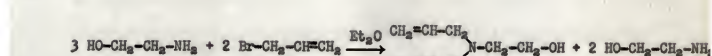
(2) $I + 2\ SOCl_2 \xrightarrow{CHCl_3} N(CH_2\text{-}CH_2\text{-}Cl)_2\text{-}CH_2\text{-}CH{=}CH_2 \cdot HCl \xrightarrow{NaOH} N(CH_2\text{-}CH_2\text{-}Cl)_2\text{-}CH_2\text{-}CH{=}CH_2$

The free amino-halide (b. 71-2°|3 mm.; n_D^{25} 1.4780) could be purified by fractional distillation; it would keep 2-3 days before quaternary formation brought about changes in the color of the material, if stored at 10-15° C.; even after several weeks' storage only a small amount

of precipitated quaternary was formed in the bottled sample.

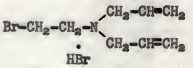
However, this compound was found to be unreactive not only toward like molecules but also toward active secondary amines. For instance, ten hours of refluxing this intermediate with an excess of diethylamine yielded none of the desired product.

Meanwhile, the preparation of N-(β-hydroxyethyl)diallylamine was accomplished through the interaction of allyl bromide and ethanolamine:



The only previous reference to this compound had been that of Ladenburg (82), who had obtained it by reacting ethylene chlorohydrin with diallylamine. He had recorded its boiling point (197°) and the preparation of its picrate, as well as the gold and platinum double salts.

The treatment of this alkenolamine with thionyl bromide yielded the hydrobromide of a new amino-halide, N-(β-bromoethyl)diallylamine:



This compound, offering an active halogen as well as two unsaturated groupings, reacted readily with secondary amines to produce four new unsaturated ethylenediamines:

(1) N,N,N',N'-Tetraallylethylenediamine

(2) N,N-Diallyl-N',N'-diethylethylenediamine

(3) N-(β-diallylaminoethyl)piperidine

(4) N-(β-diallylaminoethyl)pyrrolidine

Synthesis of N-(β-hydroxyethyl)diallylamine[1]

$$3\ HOCH_2CH_2NH_2 + 2\ Br\text{-}CH_2\text{-}CH{=}CH_2 \xrightarrow{Et_2O}$$

$$\begin{matrix} CH_2{=}CH\text{-}CH_2 \\ CH_2{=}CH\text{-}CH_2 \end{matrix}\!\!>\!N\text{-}CH_2\text{-}CH_2\text{-}OH + 2\ HOCH_2CH_2NH_2 \cdot HBr$$

In a 3-liter, three-necked, round-bottomed flask, equipped with a mechanical stirrer, reflux condenser, and dropping funnel, place 510 ml. (519 g.; 8.5 moles) of monoethanolamine, 10 ml. of water, and 200 ml. of diethyl ether. With stirring, allyl bromide is slowly added until the exothermic reaction begins; the balance of the allyl bromide (total quantity, 490 ml. — 685 g.; 5.65 moles) is dissolved in 300 ml. of ether and this solution is added to the reaction mixture at such a rate that a gentle reflux is maintained. After all of the halide has been added, 100 ml. of water is introduced and the mixture is refluxed for 0.5 hours longer, after which it is allowed to cool to room temperature and stand overnight.

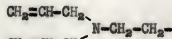
The crystallized ethanolamine hydrobromide is filtered off and the reaction mixture is extracted with 350 ml. of ether in several portions. Fractionation of the ethereal solution yields 232 g. of the pure alkenolamine; this is a yield of 58% based upon the original amount of allyl bromide used.

[1]Previously prepared by the reaction of diallylamine and ethylene chlorohydrin (82).

There is almost no forerun or residue in the distillation of the ethereal solution — the purity being such that it might be employed for the next step without further purification.

The aqueous portion of the reaction mixture contains the balance of the ethanolamine hydrobromide formed, as well as the unreacted starting material.

N-(β-HYDROXYETHYL)DIALLYLAMINE[1]



Empirical Formula ..... $C_8H_{15}NO$

Molecular Weight 141.21

Boiling Point ..... 69-71° at 6 mm.

D^{25}_{25} 0.9103

D^{25}_{4} 0.9076

n^{25}_{D} 1.4647

Mr_D :

Calcd. 43.675 (E) ; Found 42.982 ; Deviation -0.693 (E)

43.624 (V) -0.642 (V)

Appearance:

Colorless, almost odorless, liquid.

Solubility:

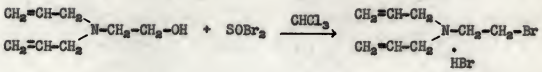
Soluble in ether; very slightly soluble in water.

Analysis; (Semi-micro Kjeldahl)

%N : Calcd. 9.92; Found 9.90; Deviation 2|1000 parts.

[1]Previously prepared by the reaction of diallylamine and ethylene chlorohydrin (82).

Synthesis of N-(β-bromoethyl)diallylamine Hydrobromide

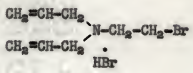


In a 1-liter, three-necked, round-bottomed flask, equipped with a mechanical stirrer, reflux condenser, and dropping funnel, place 99.4 g. (0.7 moles) of N-(β-hydroxyethyl)diallylamine, 5 ml. of pyridine, and 400 ml. of chloroform.

To this add dropwise, with efficient stirring, 70 ml. (187 g.; 0.9 moles) of thionyl bromide at such a rate that very gentle reflux is maintained. After all is added stir and reflux very gently for 2 hours; then, allow to cool and stand for 12 hours.

A solid separates in a tarry mass; no yield can be calculated on this crude product. Several recrystallizations from isopropanol-isopropylether, or from butanol-hexane, yield 78.9 g. of the pure hydrobromide; this is a yield of 39.4%, based on the amount of alkenolamine originally used.

N-(β-BROMOETHYL)DIALLYLAMINE HYDROBROMIDE



Empirical Formula ..... $C_8H_{14}NBr \cdot HBr$

Molecular Weight 285.04

Melting Point ..... 145.3-146.5°

Appearance:

Fine needles from n-butanol.

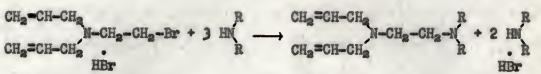
Solubility:

Soluble in water and in hot alcohols.

Analysis: (Semi-micro Kjeldahl)

%N : Calcd. 4.919; Found 4.901; Deviation 3.7|1000 parts.

General Method of Synthesis of Unsaturated Ethylenediamines



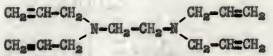
Mix three molar quantities of the secondary amine with one mole of the hydrobromide of the amino-halide. Reflux the mixture gently for 2-3 hours, with stirring; then, cool and allow to stand overnight.

Add a small amount of benzene and filter off the crystalline amine salt. Fractionate, removing any moisture present by means of the benzene-water azeotrope. The yield of the pure compound is of the order of 50-60% of the theoretical amount, based on the quantity of amino-halide used.

The hydrochloride of the N-(β-chloroethyl) derivative may also be used in this manner.

The constants of the compounds synthesized are recorded on the following pages.

N,N,N',N'-TETRAALLYLETHYLENEDIAMINE



Empirical Formula ..... $C_{14}H_{24}N_2$

Molecular Weight 220.35

Boiling Point ..... 88.2-88.7° at 1.3 mm.

D_{26}^{25} 0.8511

D_4^{25} 0.8486

n_D^{25} 1.4700

Mr_D :

Calcd. 72.864 (E) ; Found 72.450 ; Deviation -0.414 (E)

72.862 (V) -0.412 (V)

Appearance:

Colorless, mobile liquid; slight ammoniacal odor.

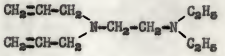
Solubility:

Soluble in common organic solvents; insoluble in water.

Analysis: (Semi-micro Kjeldahl)

%N : Calcd. 12.71 ; Found 12.69 ; Deviation 1.6|1000 parts.

N,N-DIALLYL-N',N'-DIETHYLETHYLENEDIAMINE



Empirical Formula	$C_{12}H_{24}N_2$
Molecular Weight	196.33
Boiling Point	104-6° at 18 mm.
D_{25}^{25}	0.8269
D_{4}^{25}	0.8245
n_D^{25}	1.4530

Mr_D :

Calcd. 64.562 (E) ; Found 64.365 ; Deviation -0.197 (E)

64.422 (V) -0.057 (V)

Appearance:

Colorless, mobile liquid.

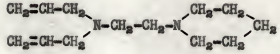
Solubility:

Soluble in common organic solvents; only very slightly soluble in water.

Analysis: (Semi-micro Kjeldahl)

%N : Calcd. 14.27 ; Found 14.17 ; Deviation 7/1000 parts.

N-(β-DIALLYLAMINOETHYL)PIPERIDINE



Empirical Formula	$C_{13}H_{24}N_2$
Molecular Weight	208.34
Boiling Point	66.8-67.0° at 0.2 mm.
D_{25}^{25}	0.8847
D_4^{25}	0.8821
$n^{25}D$	1.4780

Mr_D :

Calcd. 66.980 (E) ; Found 66.856 ; Deviation -0.124 (E)

67.057 (V) -0.201 (V)

Appearance:

Colorless, mobile liquid.

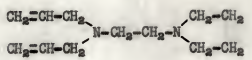
Solubility:

Soluble in common organic solvents; very slightly soluble in water.

Analysis: (Semi-micro Kjeldahl)

%N : Calcd. 13.45; Found 13.39; Deviation 4.5|1000 parts.

N-(β-DIALLYLAMINOETHYL)PYRROLIDINE



Empirical Formula ..... $C_{12}H_{22}N_2$

Molecular Weight 194.31

Boiling Point ..... 78.8-79° at 2.2 mm.

D_{25}^{25} 0.8798

D_4^{25} 0.8772

n_D^{25} 1.4741

Mr_D :

Calcd. 62.363 (E) ; Found 62.264 ; Deviation -0.099 (E)

62.410 (V) -0.146 (V)

Appearance:

Colorless liquid—turning slightly yellow on standing.

Solubility:

Soluble in common organic solvents; insoluble in water.

Analysis: (Semi-micro Kjeldahl)

%N : Calcd. 14.42 ; Found 14.33 ; Deviation 6.2|1000 parts.

SUMMARY

Synthesis of methylenediamines has been carried out in aqueous medium in the presence of both acidic and basic catalysts. In this manner, two new compounds of this type have been prepared. Further modification of the ordinary reaction procedure has allowed the preparation of a new dimethylenetriamine.

The molar refractions of all of these compounds, as well as of a series of previously-reported methylenediamines, have been investigated. The deviation of their observed Mr_D values from those calculated is explained relative to their possible electronic structure.

One new carbon-substituted methylenediamine and two new propenediamines are prepared by the reaction of secondary amines with aldehydes other than formaldehyde.

Similar reactions attempted with amino-acetals and with dialdehydes are explained.

Four new ethylenediamines are prepared by the interaction of a new amino-halide with secondary amines. Since the observed molar refractions of these substances also deviate from the calculated values, an attempt is made to explain the deviation on the basis of their modified electronic structure.

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BIOGRAPHICAL ITEMS

Mr. Norman J. Lewis was born in St. Petersburg, Florida, on July 6, 1918. He attended St. Petersburg Junior College during the years of 1935 and 1936, beginning work toward the Bachelor of Science degree. During the period 1936-1943 he was employed by the U. S. Post Office Department, North Carolina resort hotels, and finally became manager of the Tampa, Florida, branch office of a wholesale company. He resigned this position early in 1943 to volunteer for service with the United States Naval Reserve; this tour of duty lasted until December 1946. The following February he enrolled at the University of Florida. Upon completion of the prescribed curriculum, he received the degree of Bachelor of Science in Chemistry with High Honors in September 1947. Graduate study was begun at once, leading toward the degree of Doctor of Philosophy. This degree was awarded in August 1951.

He has served as an undergraduate assistant in the Department of Chemistry for one year, a graduate assistant for one and one-half years, and has held a research fellowship under the Office of Naval Research for three years. He is a member of Gamma Sigma Epsilon, Phi Kappa Phi, and Phi Beta Kappa honorary societies.

Mr. Lewis will leave the University of Florida for employment as an organic research chemist at the Monsanto Chemical Company in St. Louis, Missouri.

COMMITTEE REPORT

This dissertation was prepared under the direction of the Chairman of the candidate's Supervisory Committee and has been approved by all members of the committee. It was submitted to the Graduate Council and was approved as partial fulfilment of the requirements for the degree of Doctor of Philosophy.

Date August 18, 1951

Dean C. Francis Byrns

Supervisory Committee:

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